Best Practice

TOPICS IN REVIEW

Cost-effective evaluation of acute viral hepatitis

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The performance of extensive serologic testing of patients who present to a primary care physician or to a hospital emergency department with possible acute viral hepatitis is not cost-effective (table). A selective serologic investigation is the most prudent approach to the diagnostic workup of this disease. We review two cases of patients with possible acute viral hepatitis to demonstrate the extra cost resulting from extensive serologic testing. In the following discussion, we review the epidemiologic features, demographics, and risk factors for the disease. We also propose a schematic, cost-effective approach to investigate whether acute viral hepatitis is present. The recommendations in this article were formulated after reviewing epidemiologic data from the Centers for Disease Control and Prevention.[1] A MEDLINE search was also conducted, and recent articles on this topic were reviewed.

REPORT OF CASES

Patient 1

A 19-year-old man had progressive anorexia and malaise, preceded by fever, for 1 week. Jaundice developed 1 day before he was seen by his physician. These symptoms developed eight days after he returned from a trip to Mexico. He denied injection drug use and was not sexually active. He was not taking any medications.

A complete laboratory evaluation revealed the following liver function test results: alanine aminotransferase, 1,200 U/L; aspartate aminotransferase, 900 U/L; total bilirubin, 77 µmol/L (4.5 mg/dL); albumin, 43 g/L (4.3 g/dL); and international normalized ratio, 1.1. Hepatitis B virus (HBV) and hepatitis C virus (HCV) serologic test results were negative for hepatitis B surface antigen (HBsAg); hepatitis B e antigen (HBeAg); and antibodies to hepatitis B core antigen of immunoglobulin M type (anti-HBc IgM), hepatitis B e antigen (anti-HBe), hepatitis B surface antigen (anti-HBs), and HCV (anti-HCV). A finding of total and IgM antibodies to hepatitis A virus (anti-HAV) confirmed the diagnosis of acute hepatitis A.

Patient 2

A 54-year-old man had the sudden onset of fatigue and jaundice. He reported having multiple sexual partners. A complete evaluation revealed the following laboratory test values: alanine aminotransferase, 832 U/L; aspartate aminotransferase, 622 U/L; total bilirubin, 67 µmol/L (3.9 mg/dL); albumin, 40 g/L (4.0 g/dL); and international normalized ratio, 1.0. Serologic test results were positive for HBsAg, HBeAg, and anti-HBc IgM; they were negative for anti-HBe and anti-HBs. Serum HBV DNA was detectable at a titer of 22.6×10^6 Eq/mL (normal, $<0.7\times10^6$ Eq/mL. These results were consistent with acute and active viral hepatitis type B. Test results that were positive for total anti-HAV and negative for IgM anti-HAV were compatible with previous, recovered hepatitis A and excluded acute viral hepatitis type A. Antibodies to HCV were not found. Laboratory data available from 1 year ago showed normal results of liver chemistry tests.

COMMENTS

The patients in both cases had a full complement of serologic tests, and patient 2 in addition had virologic tests. The epidemiologic history of these two patients might have directed a more selective use of serologic tests. In the following discussion, we identify risk factors that are useful for a selective serologic evaluation for acute viral hepatitis. The knowledge of the demographics and risk factors for acute viral hepatitis can prevent the unnecessary extra cost incurred by comprehensive serologic testing (Table).

EPIDEMIOLOGY AND DEMOGRAPHICS OF ACUTE VIRAL HEPATITIS

Viral hepatitis is a major global public health concern. It is a source of substantial morbidity and mortality, both in the United States and around the world. According to data from the Centers for Disease Control and Prevention,[1] 200,000 to 700,000 new cases of acute viral hepatitis occur in the United States each year. Of these, 32%

Table *Charges for serologic and virologic tests used in the diagnosis of viral hepatitis*

Test	Stanford University Medical Center Charge*
Hepatitis A	
IgM antibody to hepatitis A virus (IgM anti-HAV)	42
Hepatitis B	
Hepatitis B surface antigen (HBsAg)	30
IgM antibody to hepatitis B core antigen (IgM anti-HBc)	61
Hepatitis B e antigen (HBeAg)	20
Antibody to HBsAg (anti-HBs)	30
Antibody to HBeAg (anti-HBe)	20
Hepatitis B virus DNA (HBV DNA)	150
Hepatitis C	
Antibody to hepatitis C virus (anti-HCV)	
Enzyme-linked immunosorbent assay (ELISA)-2	39
Recombinant immunoblot assay (RIBA)-2	113
HCV RNA	150

*Stanford University Medical Center, Palo Alto, CA, clinical laboratory billing rates, given in 1998-1999 US dollars.

Summary points

- About 100 deaths occur in the United States each year from fulminant hepatitis A and 150 deaths from fulminant hepatitis B; hepatitis C has rarely been implicated as a cause of fulminant hepatic failure
- In 5% of adult patients with HBV infection and 85% with HCV infection, the disease becomes chronic, and in a significant percentage of these patients, cirrhosis and/or hepatocellular carcinoma will develop in two or more decades
- The presence of IgM anti-HAV in serum specimens collected during the acute or convalescent period of disease confirms a diagnosis of acute hepatitis A
- The detection of HBsAg in serum specimens of a patient with acute hepatitis strongly suggests that HBV is the cause. However, confirmation by a test showing IgM anti-HBc is required because a carrier of the HBsAg may present with a non-B type of acute hepatitis.
- Because 75% of acute viral hepatitis results from infection from either HAV or HBV, the initial laboratory investigation should include serologic tests to exclude HAV or HBV.
- Serum HCV RNA can be detected 1 to 2 weeks after the onset of infection, whereas elevated serum alanine aminotransferase levels are usually noted 4 to 6 weeks later. Antibodies to various HCV antigens can be detected, on average, 8 to 10 weeks following infection with HCV.

are caused by HAV, 43% by HBV, 21% by HCV, and 4% are classified as hepatitis type non-A, B, C, D, and E. In 1995, the new cases of acute viral hepatitis included 180,000 HAV infections, 128,000 HBV infections, and 28,000 HCV infections. From these cases, about 100 persons per year die of fulminant hepatitis A and 150 die of fulminant hepatitis B; hepatitis C has rarely been implicated as a cause of fulminant hepatic failure. Although the death rate from acute viral hepatitis is low, 5% of adult patients with hepatitis B and 85% of those with hepatitis C have chronic infection, and in a substantial percentage of these patients, cirrhosis and/or hepatocellular carcinoma will develop within two or more decades.

ETIOLOGY AND RISK FACTORS OF ACUTE VIRAL HEPATITIS

The severity of illness associated with acute hepatitis A increases with age, particularly in persons aged 40 to 50 years and older.[2,3] Children younger than 2 years rarely have jaundice or other signs of acute illness. However, nearly 70% of infected adults have clinical symptoms or jaundice.[2] Hepatitis A infection may also be more severe in patients with underlying chronic liver disease of various causes.[4] Fulminant viral hepatitis type A inherently carries a high mortality and is more common in persons older than 50 years and younger than 5 years, according to data of the Centers for Disease Control and Prevention.[2] In at least half of cases, the source of HAV infection is unknown. Other risk factors associated with HAV infection are interpersonal contact (22%-26%), day-care centers (14%-16%), international travel (4%-6%), food/waterborne disease outbreaks (2%-3%), and injection drug use (<2%).[1] For hepatitis A, some type of fecal-oral transmission is almost always involved because there is no carrier state and the virus is present in much higher titers in stool than in blood.

The HBV is a DNA virus composed of three viral antigens that induce the production of three separate antibodies. For viral hepatitis type B, transmission occurs through sexual contact—33% from heterosexual contact with persons with acute viral hepatitis or who are chronic carriers, and 16% from homosexual activity—or other exchange of body fluids (for example, 17% of cases occur through injection drug use; 2% to 3% through household contacts; and <1% through health care employment). Infectious virus can persist in dried blood on surfaces. Apparent acute hepatitis can develop in patients with chronic hepatitis B as their immune system eliminates the virus. In about 95% of adults, the acute infection resolves, with chronic hepatitis developing in only 5% of patients.

The HCV is a single-stranded RNA virus. The isolation and cloning of the HCV genome in 1989 was the first step in the development of serologic tests for the diagnosis of infection by this virus. The relative proportion of acute viral hepatitis caused by HCV is 21%.[1] The risk factors associated with the acquisition of hepatitis C are injection drug use (26%), multiple sexual partners (6%) interpersonal contact (5%), blood transfusion (5%), and health care employment and hemodialysis (1% each); 56% of cases have an unknown cause. It is known that HCV RNA is found in high titers in blood but in only low copy numbers (less than 1000 copies per milliliter) in specimens of saliva, breast milk, semen, and other body fluids. Given that only about 1 copy in 10,000 is associated with an infectious viral particle, it would require exposure to multiple milliliters of a body fluid to result in infection. Sexual transmission can occur, but the risk of transmission between monogamous partners is probably less than 1% per year. Infection with HCV can also be contracted by using contaminated needles to make skin tattoos and from intranasal cocaine use.

DIAGNOSING ACUTE VIRAL HEPATITIS

In the past few decades, our understanding of the natural history of the hepatitis viruses has greatly expanded, leading to the development of serologic and virologic tests for the accurate diagnosis of acute and chronic viral hepatitis. The serologic and virologic assays are based on the measurement of viral antigens or antibodies in the serum and molecular diagnostic techniques for the detection of viral RNA or DNA.

Acute viral hepatitis type A

The presence of IgM anti-HAV in serum specimens collected during the acute or convalescent period of the disease confirms a diagnosis of acute viral hepatitis type A. In most patients, IgM anti-HAV levels subsequently decline slowly and become undetectable 3 to 6 months after the onset of infection. Infected persons also produce IgG anti-HAV during the convalescent phase. The level of IgG anti-HAV remains detectable in serum specimens for the life of a patient, and their presence protects against reinfection. Commercially available diagnostic tests to determine the presence of IgM anti-HAV and total (IgM and IgG) HAV antibody levels in serum are reliable, offering high specificity and sensitivity.

Acute viral hepatitis type B

The commercially available assays for HBV infection include those for HBsAg, anti-HBs, total or IgG anti-HBc, IgM anti-HBc, HBeAg, and anti-HBe. The HbsAg is detectable during acute and chronic hepatitis B, and its presence characterizes ongoing infection.[5] The HBeAg is found early in the disease, and its presence indicates a high level of viral replication with an increased likelihood of infectivity. It usually disappears a short time after the appearance of its antibodies. Persistence of HBeAg for more than 8 to 10 weeks after the onset of acute hepatitis is a predictor of chronic hepatitis B. Hepatitis B core antigen is the major product of the nucleocapsid gene and is not detectable in serum specimens by conventional techniques.

During convalescence from acute hepatitis B, anti-HBs appears and indicates recovery from the infection and the development of immunity.[6] They are also induced by successful HBV vaccination and generally protect against infection. Persons who receive the HBV vaccine do not develop anti-HBc. Antibodies to hepatitis B core antigen consist of IgM and IgG antibodies and appear at the onset of hepatitis B; IgM anti-HBc disappear with recovery from acute hepatitis, while total anti-HBc is present for decades. Thus, anti-HBc are detectable in both infected patients and patients who have recovered from HBV infection. This antibody must be fractionated to distinguish between acute and chronic HBV infection. This assay is therefore helpful in diagnosing acute nfection.[7]

The anti-HBe become detectable when HBeAg is lost in acute or chronic hepatitis B.[6] It is not uncommon for patients to have undetectable levels of this antibody. In patients with acute infection, the appearance of anti-HBe is correlated with the resolution of HBV infection and the absence of clinically significant liver disease. Exceptions to this general rule do occur, most strikingly in patients with reactivated chronic HBV infection and also with HBV mutants that lack the HBeAg. In both instances, severe liver disease may be seen in patients who have anti-HBe.

The detection of HBsAg in serum specimens from a patient with acute hepatitis strongly suggests that HBV is the cause. However, confirmation by a test showing the presence of IgM anti-HBc is required because a carrier of the HBsAg may present with a non-B type of acute hepatitis.[8] When reliable serologic markers are present, the use of polymerase chain reaction to detect HBV DNA for diagnosis and/or confirmation of acute HBV infection is not a cost-effective approach.[9]

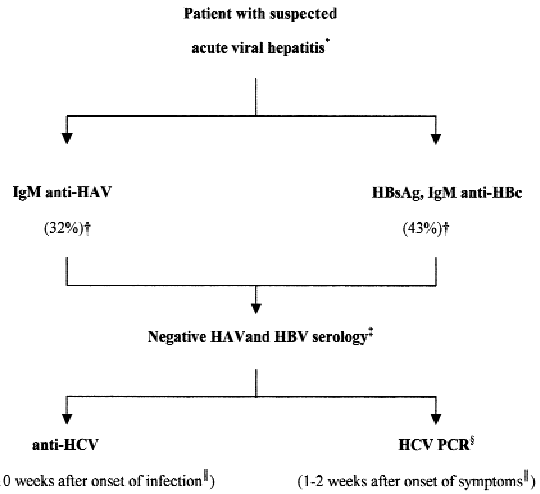
Acute viral hepatitis type C

Acute hepatitis C is usually asymptomatic and frequently subclinical.[1] Serum HCV RNA can be detected 1 to 2 weeks after the onset of infection, whereas elevated serum alanine aminotransferase levels are usually noted 4 to 6 weeks later.[10] Antibodies to various HCV antigens can be detected, on average, 8 to 10 weeks following infection with hepatitis C.

During the past eight years, progressively refined generations of assays for detecting HCV antibodies have become available.[11] The basic difference between the generations of these tests is the number of recombinant antigens included in the test. The enzyme-linked immunosorbent assay (ELISA) has been the mainstay screening test for anti-HCV. It is relatively inexpensive and has the additional advantages of technical simplicity and reproducibility. The currently available ELISA-2 may soon be replaced by a more sensitive third-generation test.[10] It is prudent to confirm a positive ELISA result for anti-HCV, particularly for low-risk persons, among whom the currently available ELISAs have a substantial false-positive rate. In the United States, the most commonly used supplemental assay is the recombinant immunoblot assay. Currently available tests have a sensitivity greater than 95% for chronic hepatitis C.[12] The test has poor sensitivity in organ transplant recipients and patients receiving renal dialysis.

COST-EFFECTIVE DIAGNOSIS OF ACUTE VIRAL HEPATITIS

A cost-effective diagnostic workup of patients with possible acute viral hepatitis is the most reasonable approach (figure).[13–15] This algorithm, however, is not applicable to patients who present with fulminant hepatic failure or who have had chronic viral hepatitis. Because 75% of cases of acute viral hepatitis result from infection with either HAV or HBV, the initial laboratory investigation should include serologic tests to exclude HAV or HBV. If the results of these studies are negative, further testing should be done to rule out acute HCV infection, which is less common. Serum HCV RNA is detectable 1 to 2 weeks after the onset of infection, whereas anti-HCV can be detected 8 to 10 weeks following infection with the virus.[10] In clinically stable patients, waiting and checking for



Algorithm for cost-effective laboratory evaluation of acute viral hepatitis

the presence of antibodies to HCV may be plausible. Checking for HCV RNA by polymerase chain reaction in all patients is not cost-effective, unless there is a known history of blood exposure. Finally, not all acute hepatitis is viral. If the initial evaluation fails to show viral hepatitis, then other causes of hepatitis, such as alcoholic hepatitis, drug toxicity, autoimmune hepatitis, or Wilson's disease, should be considered.

CONCLUSIONS

This algorithm provides a reasonable approach to the diagnosis of acute viral hepatitis and does not jeopardize patient management. It also prevents obtaining unnecessary and costly serologic tests in patients who may not have acute viral hepatitis.

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COMMENTARY

All patients with acute hepatitis must be observed until the acute liver injury resolves

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Ahmed and Keeffe point out that only a few basic viral diagnostic tests are indicated for the initial evaluation of patients presenting with acute hepatitis. This is in consideration that hepatitis A and B account for three fourths of cases of acute viral hepatitis in the United States. The presence of hepatitis A or B is sometimes heralded by arthralgias, nephritis, or urticaria, which can provide useful diagnostic clues.[1,2]

Hepatitis C should be considered in patients with a known blood exposure, but only a fraction of persons with hepatitis C have acute jaundice or other recognizable symptoms. Furthermore, when symptoms occur with acute hepatitis C, the development of hepatitis C antibodies is often delayed several weeks after the onset of symptoms. The use of viral diagnostic tests other than the basic tests for hepatitis A and B can be guided by epidemiologic risk factors.[3]

A large number of viruses and other infectious agents occasionally cause hepatitis, sometimes as part of a multisystem illness such as infectious mononucleosis or Hantavirus infection. Hepatitis E is a form of acute viral hepatitis found in the Indian subcontinent and occasionally in Latin America.[4] In a patient without a pertinent travel history or a history of immunosuppression, it is usually not useful to pursue these less common diagnoses.

Not all patients presenting with acute elevation of aminotransferase levels have viral hepatitis. Many other serious, treatable conditions can masquerade as viral hepatitis. A hepatic drug reaction can be lethal if the offending agent is not stopped. Acetaminophen can cause intentional or